



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/757,827

01/15/2004

Michael R. Rosen

68262-A/JPW/PJP/NS

5518

7590

05/24/2006

Cooper and Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER

SINGH, ANOOP KUMAR

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 05/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/757,827	Applicant(s) ROSEN ET AL.	
	Examiner Anoop Singh	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 March 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 20,49-51,54-57 and 59 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20,49-51,54-57 and 59 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of the invention of group IV (claims 20, 23-38, 49-50 and 64) filed on October 24, 2005 was acknowledged. Applicant's argument of examining method for treating cardiac condition using composition of for ion channel transfer comprising stem cell modified with a compound (group VI, claim 51-62) with elected group were found persuasive, therefore invention of group IV and VI directed to composition and method of treating cardiac condition were rejoined for the examination purposes.

2. Applicant's amendment filed on March 6, 2006, has been received and entered. Claims 1-19, 21-48, 52-53, 58 and 60-64 have been canceled. Claims 20, 49-51, 54-57 and 59 have been amended.

Claims 20, 49-51, 54-57 and 59 are under consideration in the instant application.

Claim Rejections - 35 USC § 112- Second Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1632

4. Applicant's amendment in claims 49, 50, 54 and 55 are found persuasive.

Therefore, Claims previously rejected under 35 USC § 112 as being vague and indefinite are withdrawn.

New- Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 20, 49-51, 54-57 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118(a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In the instant case, the recitation of limitation "effective" is considered new matter. Applicants do not point to the specification for the specific support of the claimed amendments. Upon further review of the instant specification, examiner could only find support of condition that would express HCN2 in an amount sufficient to create ion channel. Since a minimal amount may be sufficient which would be different in scope if changed to an effective amount to create ion channel or inducing

Art Unit: 1632

pacemaker current. Furthermore, specification provides support to amount sufficient and not to the effective as recited in claim 20, 51, 57 and 59.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981) teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time application was filed... If a claim is amended to include subject matter, limitation or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes, "When an amendment is filed in reply to an objection or rejection based on U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendment made to the disclosure".

To the extent the claimed compositions and or method are not described in the instant disclosure, claims 20, 49-51, 54-57 and 59 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since the applicants disclosure do not teach a composition and/or method that is adequately described in the specification. As described before, the specification does not provide

Art Unit: 1632

adequate guidance on determining what is included or excluded by the claims as amended and therefore an artisan of skill would require undue experimentation to practice or make and/or use the invention.

7. Claims 20, 49-51, 54-57 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The amended claims recite a composition of mesenchymal stem cell (MSC) comprising HCN2 and a method of expressing a functional ion channel in a syncytial structure comprising a MSC incorporated with a nucleic acid in amount effective to express HCN2 ion channel in heart. Claim 50 limits the syncytial structure to include heart. Subsequent claims recite a method of treating a cardiac condition in any subject, which comprises contacting a cell of heart with the mesenchymal stem cell incorporated with a HCN2 in an amount effective to increase the pacemaker current for the treatment of cardiac rhythm disorder. The claims are also drawn to a method of inducing pacemaker current in the heart of any subject by delivering the mesenchymal stem cell incorporated with HCN2 that express ion channel. The invention also encompasses a method of inducing pacemaker current in a cell which comprises contacting a cell with the composition comprising a mesenchymal stem cell incorporated with a nucleic acid

Art Unit: 1632

which encodes HCN2 in an amount effective to induce a pacemaker current in the cell, thereby inducing a pacemaker current in the cell.

It is emphasized that although claim 20 is drawn to a composition for ion channel comprising a mesenchymal stem cell incorporated with nucleic acid encoding HCN2 in an amount effective to create ion channel, however it has also been analyzed for its intended use in the treatment of heart failure and other cardiac disorders.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge

pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

The aspects considered broad are: breadth of subject population, method of treating any cardiac rhythm disorder in any subject, any route and method of administering the composition subsequently limiting to injection and catheter.

It is noted that as instantly recited, the claimed invention reads on broad genera of cell therapy by delivering a composition comprising MSC incorporated with nucleic acid encoding a HCN2 protein into a subject, that is generally not enabling in humans due to problems with, *inter alia*, homing effect of mesenchymal cell, difficulty in obtaining homogenous population of human MSC to elicit therapeutic effective response. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in isolating and characterizing mesenchymal stem cell from any subject, (ii) how administering a composition of MSC comprising HCN2 would have resulted in the treatment of all cardiac rhythm disorder. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of cell therapy *in vivo* in humans is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced in any subject. As will be shown below, broad aspects were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient

guidance to practice the claimed invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The specification as filed provides a general description of pacemakers and cardio-active drugs and the summary of the inventions (pp 1-6). Pages 7-9 describe brief description of figures showing transfer of Lucifer yellow dye from stem cell to HeLa cell and coupling and ionic dye transfer between stem cell and a canine cardiomyocyte. Page 10-18 provides a detailed description of the invention, preferred embodiments and definitions of terms. Page 19-34 discloses a proposal in five different phases that includes for expression, regulation of pacemaker gene *in vitro*, *in vivo*, and in isolated tissue.

Applicant's examples on pages 7-9 disclose the transfer of Lucifer yellow dye from stem cell to HeLa cells transfected with Cx43 showing transfer of dye by diffusion through gap junction. Figures 3(A-C) show coupling and ionic and dye transfer between stem cells and a canine cardiomyocyte while Figure 4(A-B) demonstrate stem cell coupling with HeLa cells. Figure 5, 6 and 8 show human mesenchymal stem cell and inward rectification, needle survival and transient transfection of MSC. Figure 8 and 9 disclose HCN2 incorporate stem cell could generate pacemaker current while Figure 10(A-E) demonstrate expression of pacemaker current in canine ventricle *in situ* as a result of implanting mesenchymal stem cell having the HCN2 pacemaker gene.

In summary, the specification does not provide any specific guidance to practice claimed invention in humans because the specification as filed does not teach how homogenous population of MSC from any source would be obtained and characterized.

Art Unit: 1632

The specification also does not provide any specific marker that would distinguish human MSC that could be used to express HCN2 for transplantation by any route for the treatment of any cardiac rhythm disorder. Furthermore, It is noted that the specification does not provide any guidance as to what is meant by effective amount, since it would be subjective to variable interpretation depending on the artisan.

As a first issue, the claim 20 and subsequent dependent method claims embrace a composition for ion channel transfer that comprises a mesenchymal stem cell incorporated with a nucleic acid encoding HCN2 ion channel in an amount effective to create an ion channel. The specification contemplates that hMSC can be isolated from donors. The specification also asserted that hMSC are easy to culture and one could easily test cell purity by flow cytometry (pp 30, lines 18-29). However, the specification has provided no guidance how to obtain purified homogenous population of hMSC. Prior and post filing art teaches that a number of fundamental questions relating to the biology of undifferentiated MSCs remain unanswered. These involve the homogeneity of the cells used for therapy, the survival and homing capacity of the cells to host tissues following transplantation, and the differentiation potential of these cells *in vitro* versus *in vivo* (Boheler, 2004, J Physiol 554, pp 592, col. 1, para 2). In addition, Boheler state, “[m]ultipotent hMSCs have been isolated in clonal assays, but the isolated clones did not differentiate with an equal degree of plasticity. suggest that unique subpopulations may be present in hMSC cultures that preferentially differentiate to selected mature cell types”. It is noted that Boheler emphasize on “further basic research for the use of cell surface or functional markers that may prove critical to fully

Art Unit: 1632

exploit hMSC for therapeutic purposes". Thus, it is clear without any specific guidance on how to obtain and characterize homogenous hMSC and merely a general description of method of obtaining human MSC is not enabling for the claimed composition intended for the treatment of cardiac rhythm disorder in humans. Because of the art, as shown above, suggesting problems associated with obtaining homogenous MSC that is characterized by cell surface markers. Artisan could not predict, in the absence of proof to the contrary, that such a method as recited in instant application would be efficacious in the treatment of any cardiac rhythm disorder. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because of the art of MSC transplant *in vivo* is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

As a second issue, the scope of invention as claimed encompasses a method for inducing expressing functional ion channel in syncytial structure, inducing pacemaker current and treating a cardiac rhythm disorder in a subject by disclosed genetically modified MSC composition. It has been difficult to predict the efficacy and outcome of a transplanted hMSC because several factors that governs the therapeutic potential of these cells *in vivo*. For instance, Javazon et al state "little has been demonstrated regarding the MSC *in vivo* biology and therapeutic potential (Experimental Hematology, 32, 414-425, 2004). It appears that site-directed administration of MSCs can result in engraftment and integration of MSCs under specific circumstances however, few studies have examined whether donor cells engraft and differentiate into particitory cells

Art Unit: 1632

or if persistence of donor cells is due to fusion events and less well defined effects are observed after systemic administration of MSCs" (pp.417, col. 1, under *in vivo* characteristics of MSCs). Javazon et al further reports that in reality the evidence supports non-specific lodgment of MSCs in multiple vascular beds with persistence of very small number of donor cells in various tissues (pp 417, col. 1-2 under *in vivo* characteristics of MSCs). Despite the observations of persistence of MSCs after infusion into allogenic or xenogenic hosts, little is known regarding host immune response to MSCs (Javazon et al pp 417, col. 2, last paragraph). The immunology of MSCs remains a poorly understood and *in vivo* studies of immunogenicity of MSC are needed since long term culture of MSC in presence of fetal bovine serum (FBS) may change the immunogenicity of MSC (Javazon et al pp418, col. 1, para 1). Barry et al (The International Journal of Biochemistry of Cell Biology, 36, 568-584, 2004), while reviewing the state of MSCs in transplantation cell therapy concluded that there are several aspect to the implanted cell host cell interaction that need to be addressed before we can fully understand the host immune response to implanted cells. The homing mechanism that guide delivered cells to the target site and the differentiation of implanted cells under the influence of local signals (abstract and pp 580, col. 2, conclusion).

Additional important issues of MSCs cell therapies are the therapeutic efficacy of the transplanted cells and the mechanism of engraftment, homing and *in vivo* differentiation. Gepstein (Expert Opinion Biol Ther, 5(12); 1531-1537, 2005), while reviewing the state of stem cell as biological heart pacemaker and providing and expert

opinion reports that one limitation relates to the possible differentiation of the MSCs within the heart into unwanted cell lineages, such as bone and cartilage (pp 1534, col. 1, last para). In addition, issues relating to the number and distribution of the surviving grafted cells within the heart, and the degree of coupling between the host and donor cells may have important consequences to the function of these cells (pp 1534, col. 1, last para). Beyer Nardi et al (Handb Exp Pharmacol, 174, 249-282, 2006) also report that for MSCs little is known about their known properties *in vivo* and the task will not be easy, because at present tracking the fates of ex vivo manipulated MSCs after their systemic delivery in animal models may lead to skewed results (pp 273). The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in a human by administering composition comprising any MSC via any route, since non-specific engraftment and host immune response are also critical determinant for the successful pacemaker activity. An artisan would have to carry out extensive experimentation to make use the invention, and such experimentation would have been undue because non specific engraftment and host immune response after hMSC is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

As a third issue, instant methods embrace induction of pacemaker current in order to treat any cardiac rhythm condition. While summarizing the work of Heubach Boheler et al (J Physiology, 554, 3, 592) state "Heubach et al (2004) identified and characterized several inward and outward cell currents typically present in a

Art Unit: 1632

'homogeneous' population of MSCs obtained either from primary cell isolates or from a commercial source. The authors demonstrate the presence of two outward currents (I_r and I_s) in the majority of hMSCs, and the I_r current was further characterized as a large-conductance voltage- and Ca^{2+} -activated K^+ current. Inward currents were, however, only present in a subpopulation of hMSCs". Boheler et al conclude that the finding that hMSCs displayed a mixed distribution of channels argues for a heterogeneous cell population. It is clear from the teaching of Heubach et al that only a unique subpopulation may be present in hMSC culture that preferentially differentiate to selected mature cell type (Boheler, pp 593, col. 3, para. 2). In fact, even Gepstein et al, who evinces an optimistic outlook for hMSC therapy, also raise a number of issues including degree of coupling between the cell types. It is emphasized that Gepstein et al describe "pacemaker function of these cells is result of combination of activity of a number of ionic current. Thus, over expression of the HCN current alone will not fully recapitulate all the properties of SA node cell (pp 1534, col. 1, para 4 bridging to col. 2, para1)". Thus, it is evident from the art of record that in absence of any clear guidance in the specification a number of other variables could play a critical role in inducing pacemaker current in a cell or heart for the treatment of all different type of cardiac rhythm disorder.

As a final issue, the claimed invention embrace a method wherein contacting a MSC is effected by injection and microinjection or catheterization. Boheler et al (J Physiology, 554, 3, 592) while discussing the outcome of MSC therapy raise number of question concerning best way to introduce (local or systemic) cells for therapeutics and

Art Unit: 1632

the survival and homing capacity of the cells to host tissues following transplantation.

Gepstein reports for cell therapy approaches determining the optimal way for the delivery of the cell controlling their survival following transplantation, assuring appropriate integration of the cells with the host tissue and developing means to control the required effect all important obstacle for the future use of these strategies. In addition, issue related transplanted cells as well as their potential to differentiate into undesired cell lineages should be addressed (pp 1536). In fact, in a post filing art, Applicants describe the limitation of delivery of modified hMSC to free wall myocardium that is not an optimal site of contraction. It is disclosed that catheter approaches to insert pace maker gene have more ordered and normal activation and contraction. However, Applicants state that this approach was not available to hMSC transplant due to problem associated with cell size and potential of injury to the cell. The cited art clearly suggest that administering MSC by catheter was mere a hypothesis since extent of cell injury and potential of administering MSC by catheter was not available even after filing of instant application. In view of foregoing discussion, it is evident that unpredictability related to undesired cell lineages differentiation and unordered activation and contraction would have also potentially induced cardiac arrhythmia as discussed in previous office action dated 12/7/2005 (Mocini et al and Zhang et al). An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because of plurality of variables associated with mesenchymal stem cell transplant therapy for a cardiac

rhythm disorder and specification fails to provide any guidance as to how the claimed method would have been practiced in humans.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. An artisan of skill would have required undue experimentation to practice the invention because the art of cell therapy in general for the treatment of cardiac condition was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to Arguments

8. Applicant arguments filed on 3/06/2006 have been fully considered but they are not persuasive. Applicant in their argument on page 5, second paragraph state that stability of HCN2 expression in stem cell transfected as described in specification and reported by Plotnikov et al (Circulation, 2005, 112, II-126, Exhibit A) show MSC transfected with HCN2 and introduced in canine hearts *in situ* induced pacemaker function that is stable for at least 6 weeks and all animal show stable pacemaker activity for the duration of the study. The Applicants further agree that instant application and cited exhibits (B and C) specifically demonstrate engrafted stem cell formed gap junction (page 6, para 1). In addition, Applicants also assert that specification provides experimental data confirming the HCN2 incorporated stem cell generate pacemaker

Art Unit: 1632

current that could be used in a method of treating a cardiac rhythm disorder in a subject (page 6, para. 2 and 3 bridging to page 7 para 1).

In response, it is emphasized that amended claims of instant inventions recite a composition and methods intended for treating cardiac rhythm disorder in any subject including humans by administering the composition of MSC via any route to treat any cardiac rhythm disorder. Claims 49, 57 and 59 recite method of expressing functional ion channel in a syncytial structure, inducing current in a subject or in a cell respectively, however, that are intended to treat similar condition as disclosed in claim 51. The specification provides a description that is not sufficient to provide enabling support because the claimed therapy method cannot be actually reduced to practice until the skilled artisan is provided by sufficient guidance to how to obtain and characterize homogenous population of human mesenchymal stem cells. In addition, cited arts in this office action clearly show the variability and problems associated with obtaining homogenous population of hMSC, homing effect, immune response and differentiation and engraftment of these cells in any *in vivo* therapy (supra). These methods would have required undue experimentation because neither the specification nor the art of record teaches specific guidance in this regard. It is further emphasized that post filing cited art cannot be used for the enabling support of the instant claims as cited arts uses method that is different from the instant disclosure and does not provide guidance to other issues raised in this office action. In the instant case, cited references teach hMSC are obtained from commercial source. Plotnikov et al (Exhibit A) use 1.5×10^5 - 1.02×10^6 hMSC for injection into left ventricle (LV) wall of canine. These subjects are

Art Unit: 1632

monitored for 42 after implantation of hMSC. It is also noted that injection in LV induces transient apoptosis. The disclosure in instant application provided no guidance in terms of number of cells that would be effective in inducing current in any subject. Similarly, Potapova et al (Exhibit B) administered 10^6 hMSC containing HCN2+GFP in LV of canine heart, while instant disclosure provided no such detail. Upon further review, it is also noted that Potapova describe that MSC were delivered to the free wall myocardium, which is not an optimal site for ordered contractions. It is also disclosed that in an another study Applicants have used catheter to overcome this problem, however, once again method disclosed by Plotnikov et al (Circulation, 2004; 109: 506-512) was not disclosed in instant application at the time of filing of this application. Therefore, any study in canine model that uses specific number of hMSC delivered via catheter or any site other then one disclosed in instant application cannot be enabling support. Furthermore, it is art recognized fact that even commercial hMSCs displayed a mixed distribution of channels (supra), suggesting more characterization of MSC is required. In absence of any such explicit teaching, a skilled artisan would have to determine the various specifics and would have to perform undue experimentation to obtain homogenous population of MSC from same or different donor. These would have required undue experimentation because neither the specification nor the art of record provided any specific guidance in this regard.

On page 8, in the first and second paragraph, applicants argue that instant ground of rejection appears to be based on the absence of an optimized protocol in the specification for performing claimed methods. In response, it is emphasized that

Art Unit: 1632

previous rejection was based on lack of disclosure of specifics of stem cell that are required to be engrafted in heart for pharmacological response for the treatment of any cardiac condition. Further the specification also provided no correlation between number of stem cell delivered that are engrafted at the site of action to number of cells that are relocated to other places (previous office action, page 7, para. 3). It is noted that the amendment in instant claims now recite composition comprising modified MSC. The issue of effective number of cell engraftment in heart is critical to overall effect contemplated in the specification. It is art recognized fact that there are several variables such as homing, degree of engraftment and differentiation of cells to other lineage may play a critical role during MSC transplantation as discussed earlier (supra). These factors are not optimization factors rather are directly relevant to the therapeutics of the claimed invention.

Applicant's arguments on page 6 (para 6) and page 10 (para 1) with respect to claims 51-53, 57 and 59 are moot in view of the cancellation of claims 52-53 and amendment in claim 51, 57 and 59.

On page 9 and 10, applicants argue that safety issue raised by the Examiner fall within the province of the Food and Drug Administration and not USPTO. In response, it is emphasized that Examiner had no intention to raise any toxicity or safety issue arising from cell transplantation. The discussion is merely intended to address problems that are associated with stem cell therapy. Furthermore, Examiner was raising the issue of arrhythmia seen after stem cell transplant because an arrhythmic episode after cell therapy would be detrimental and defeat the sole purpose of any potential of MSC in the

Art Unit: 1632

treatment of any cardiac disorder. The amended claims now recite undifferentiated adult MSC, however, problem of potential differentiation to cell of other lineage still exists as discussed before (*supra*).

Claim Rejections - 35 USC § 112 (Written Description)

9. Applicant's amendment in claims 20, 49-57 and 59 are found persuasive.

Therefore, claims previously rejected under 35 USC § 112 –Written description are withdrawn.

Double Patenting

10. Claims 20, 49-51, 54-57 and 59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-59 of copending Application no 10/342506 (US Patent Publication no 20040137621). Even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass similar composition and a method of inducing current and a method of treating a cardiac condition by introducing a composition of mesenchymal stem cell comprising a nucleic acid encoding HCN2 into a subject.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Art Unit: 1632

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 102

11. Applicant's amendment in claim 20 is found persuasive. Therefore, claims previously rejected under 35 USC § 102 are withdrawn.

New Claim Rejection - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marban et al (US Patent application Publication no US2004/0254134, publication date 2/16/2004; effective filing date 2/29/2002) and Heubach et al (Circulation, 106 (19) 2002, suppl. pp II-68), Jansen et al (US Patent no 6979532, dated 12/27/2005, effective filing date 2/12/2000).

Claim 20 is drawn to a composition for ion channel transfer, which comprise mesenchymal stem cells incorporated with a nucleic acid encoding HCN2 in an amount effective to create ion channel in the cell.

Heubach et al teach injection of autologous mesenchymal stem cell into the heart. Heubach characterized ion current and expression of 20 cardiac ion channels in human MSC obtained from bone marrow aspirate. Heubach et al also teach high mRNA level of HCN2 in MSC cells. Heubach concluded that undifferentiated MSC expresses a consistent pattern of ion channel mRNA and the outward current seen were likely to be carried by K⁺ channel. It is noted that Heubach state novel therapeutics strategies of heart failure include the injection of autologous mesenchymal stem cell into the heart (abstract). However, Heubach do not teach MSC comprising HCN2.

Marban et al disclose that composition of modified cells could be administered to induce or modulate pacemaker activity of cells or a subject. It is noted that source of modified cells are cardiac myocardial cells generated from differentiated stem cells, such as embryonic bone marrow cells. The stem-cell-derived cardiomyocytes exhibiting pacemaker function then may be implanted such as by catheter or injection to targeted

Art Unit: 1632

cardiac tissue (pp10, paragraph 121). Marban also teach genes that could be used to affect cardiac firing rate includes ion channels including HCN channels (pp6, paragraph 64). The teaching of Marban et al encompasses HCN2 channel as different isoform of HCN channel were known in the art and Marban et al intend to use different HCN channels to affect firing rate of heart. However, Marban et al do not teach using a composition of MSC comprising HCN2.

Jansen et al teach a process comprising providing mammalian cells that express a hyperpolarization-activated cation channel including HCN2 and determining the membrane potential of the cells (col. 5, lines 5-25, col. 5, lines 60-63 and claims 1, 21 and 31. However, Jansen et al do not explicitly teach a composition of MSC comprising HCN2.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the cells taught by Heubach et al by expressing a nucleic acid encoding HCN isoforms taught by Marban et al, for expressing ion channel genes in stem cell at sufficient level for pacemaker activity. Marban provided motivation to transfect cells with HCN channels gene as, it could be used to affect cardiac firing rate. The skilled artisan would be motivated to use different isoforms of HCN including HCN2 as Jansen had already shown that HCN2 could be expressed in mammalian cells to determine membrane potential and Marban had disclosed the usefulness of HCN channel gene in pacemaker activity. Furthermore, Heubach et al had already shown that mesenchymal stem cells express consistent pattern of ion channel and could be directly administered to heart for novel therapy for heart failure (abstract).

One who would practice the invention would have reasonable expectation of successfully producing a composition comprising mesenchymal stem cell incorporated with HCN2 or other ion channel gene because the art had already shown that HCN2 and other ion channel isoform could be expressed to different cardiac or stem cell for pacemaker activity. One of ordinary skill in art would have been motivated to combine the teaching of Heubach, Marban and Jansen because a composition comprising mesenchymal stem cell expressing HCN2 would have provided biological pacemaker activity and thus provide a novel therapy for heart failure.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Response to Arguments

14. Applicant's arguments with respect to claims 20, 23, 25, 27, 31, 33 and 64 have been considered but are moot in view of the amendments in claim 20 and new ground(s) of rejection.

15. No Claims allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you

Art Unit: 1632

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Anoop Singh, Ph.D.
AU 1632

Joe Winters
AU 1632